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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,588	07/20/2001	David C. Klein	14014.0342U2	3159

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,588	KLEIN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2004 and 07 January 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,10,11,15-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,10,11,15-17,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed September 21, 2004 has been entered. The specification has been amended as requested.

The Declaration of Inventorship filed April 30, 2003 has been received and entered into the file.

The amendment filed January 7, 2003 (hereinafter referred to as "the response") has been entered. Claims 1, 5, 6, 10, 11, 15, 17, and 19 have been amended. Claims 4, 9, 12-14, and 18 have been cancelled.

Accordingly, Claims 1-3, 5-8, 10, 11, 15-17, 19, and 20 remain pending in the instant application.

The rejection of Claims 12-14 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the cancellation of these claims.

The rejection of Claim 17 under 35 U.S.C. 112, second paragraph, as indefinite, is withdrawn in view of the amendment to the claim.

The rejection of Claims 1-3, 6-8, and 15-17 under 35 U.S.C. 103(a) as being unpatentable over Khalil et al. (June 1998) is withdrawn in view of Applicants' arguments at page 15, paragraph 1 of the response.

The rejection of Claims 1-3, 6-8, and 15-17 under 35 U.S.C. 103(a) as being unpatentable over Khalil et al. (November 1998) is withdrawn in view of the amendments to the claims.

Preliminary Matters

Throughout the response, Applicants refer to the Office Action dated December 10, 2001. The only Office Action on the merits in the instant application, however, is dated October 2, 2002. Since the parent case 09/374,742 was abandoned on July 26, 2001, there is likewise no Office Action dated

December 10, 2001 in that case. Thus, where Applicants refer to "the Office Action dated December 10, 2001", it is assumed that Applicants intended to refer to the Office Action dated October 2, 2002.

Applicants' response refers to three 37 CFR 1.132 declarations of Dr. Klein as Exhibits A, B, and C. The response further states that Exhibits A and B are copies of two declarations filed in the parent application 09/374,742. However, the only 37 CFR 1.132 declaration received with the response of January 7, 2003 is the declaration dated January 8, 2001. It is assumed that this is the declaration that Applicants are referring to as Exhibit B in the response, although the declaration is not labeled as Exhibit B. It is further assumed that the declaration of May 8, 2000 (filed in the parent case) is the one referred to as Exhibit A. For purposes of preparing this Office Action, the Examiner referred to the declaration of May 8, 2000 present in the parent application. Applicants should note, however, that this declaration is not of record in the instant application and Applicants are advised to resubmit a copy of the appropriate declaration if Applicants wish to have it of record in the instant Application. Likewise, Exhibit C, which Applicants refer to as a new 37 CFR 1.132 declaration of Dr. Klein is not present in the instant application and therefore is not available to the Examiner. Applicants are advised to resubmit Exhibit C if Applicants wish to have it of record in the instant Application. However, Applicants are reminded that declarations and other evidence submitted after final rejection are not considered timely and therefore will not be considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-8, 10, and 11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* applications of the claimed methods, wherein an N-

bromoacetylated acetyl acceptor substrate or an N-chloroacetylated acetyl acceptor substrate is introduced into a cell expressing an acetyltransferase, does not reasonably provide enablement for *in vivo* applications of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of producing a bisubstrate inhibitor in a cell, a method of inhibiting the activity of an acetyltransferase in a cell, and a method of inhibiting melatonin production in a cell. The claims read on both *in vivo* and *in vitro* applications of the methods.

In view of the data presented in the Declarations of Dr. David Klein filed May 8, 2000 and January 8, 2001, the scope of enablement has been expanded to include any acetyltransferase and additional substrates as recited in the present claims.

As noted at page 4 of the Office Action of October 2, 2002, the specification fails to provide an enabling disclosure for *in vivo* applications of the claimed methods because the *in vivo* effects of the various compounds recited in the claims are unknown. No guidance is offered regarding the *in vivo* effect of introducing an acetyltransferase inhibitor into a cell. The specification does not offer any guidance for the manner of using any of the compounds such as those recited in the claims *in vivo*. The specification does not offer any working examples to demonstrate *in vivo* applications of the claimed methods. The specification teaches that the only use for the *in vivo* applications is to provide therapeutic benefit, to limit adverse effects of certain drugs, or to improve the efficacy of certain drugs. However, the specification does not teach how to use the claimed methods to achieve any of these effects. Furthermore, no guidance is provided with regard to how the compounds would be administered or how often the compounds should be administered to produce the desired therapeutic effect. Moreover, the specificity of the inhibitor is essential for the *in vivo* operability of the claimed methods, yet the specification does not offer any guidance regarding the specificity of the inhibitors to be used in the claimed methods. Further

lacking is an assessment of the toxicity of the compounds contemplated for use *in vivo*. In the absence of specific guidance, one skilled in the art would have been required to engage in undue experimentation to practice the claimed methods *in vivo*.

At pages 7-10 of the response, Applicants argue that the specification is enabling for substrates other than N-bromoacetyltryptamine and is further enabling for acetyltransferases other than AANAT. These arguments are answered by the expanded scope of enablement indicated herein above. The declaration of May 8, 2000 (designated Exhibit B in the response) convincingly demonstrates enablement for acetyltransferases other than AANAT. Thus, the broader scope of the claims, as indicated above, would be considered enabled for claims limited to *in vitro* applications or methods.

At pages 11-13 of the response, Applicants argue that the specification provides an enabling disclosure for *in vivo* methods and *in vivo* cells. The arguments refer to Exhibits B and C. Exhibit B and the arguments relying thereon have been fully considered. Where the arguments rely on Exhibit C, the arguments have been fully considered. However, Exhibit C itself is not of record and has not been considered. The Examiner cannot comment of evidence that is not of record. Applicants assert that Exhibits B and C relate to experiments performed in rats, where BAT was administered to rats (at 60 mg/kg or 10 mg/kg) treated with isoproteronol (to increase melatonin production) and the pineal gland was removed and assayed to determine the amount of melatonin present. Applicants argue that the results presented in Exhibit B demonstrate significantly lower levels of pineal melatonin after BAT administration and therefore demonstrate that the claimed methods work *in vivo*. Applicants further argue that the results presented in Exhibit C demonstrate that although BAT treatment did not reduce pineal melatonin in control rats, BAT treatment did reduce pineal melatonin in isoproterenol-treated rats and therefore, Applicants conclude, the present application is fully enabled for practice of the claimed invention *in vivo*. However, Applicants are reminded that it is well established in our law that the specification must teach how to use the claimed methods consistent with the utility asserted in the

specification. The instant specification asserts that the claimed methods can be used to provide a therapeutic benefit, to limit adverse effects of certain drugs, or to improve the efficacy of certain drugs. However, the specification does not teach how to use the claimed methods to achieve any of these effects and the declarations do not address this issue because the experiments described therein used healthy rats rather than disease models. Thus, no treatment effect is taught and there is no evidence presented to show that the decrease in melatonin synthesis would be sufficient to result in a treatment effect in a diseased animal, limit adverse effects of certain drugs, or improve the efficacy of certain drugs, which are the only utilities asserted in the specification for inhibiting melatonin production *in vivo*. The specification does not provide specific guidance for producing these *in vivo* effects. Thus, the specification fails to provide an enabling disclosure for *in vivo* applications of the claimed methods.

Claims 15-17, 19, and 20 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated cell comprising a bisubstrate inhibitor, wherein the bisubstrate inhibitor is synthesized from an N-bromoacetylated acetyl acceptor substrate or an N-chloroacetylated acetyl acceptor substrate for an acetyltransferase present in the cell and CoA, does not reasonably provide enablement for a cell residing *in vivo* or for a bisubstrate inhibitor **comprising** an N-bromoacetylated acetyl acceptor substrate or an N-chloroacetylated acetyl acceptor substrate, since the bisubstrate inhibitor does not actually **comprise** the bromoacetyl group or chloroacetyl group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims have been amended so that they now recite that the bisubstrate inhibitor "comprises a N-bromoacetylated acetyl acceptor substrate or a N-chloroacetylated acetyl acceptor substrate." However, in view of the teachings of the specification, it is clear that the bisubstrate inhibitor does not actually **comprise** the bromoacetyl group or chloroacetyl group since the bromo- and chloro- substituents

are leaving groups in the context of the enzymatic reaction. This is new issue raised by Applicants' amendment to the claims.

The arguments relating to the *in vivo* aspect of this rejection, presented at pages 11-13 of the response, have already been addressed herein above.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER